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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,242	07/13/2001	Peter Eriksson	003300-798	9923

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,242	ERIKSSON ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *5,6,8,15-22 and 24-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,9-14 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1, 5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 7, filed 5/27/03, is acknowledged. The traversal is on the ground(s) that 1) all of the inventions of the different groups share a common technical feature that is a contribution over that of the prior art (i.e. methods of introducing substances into mammalian stem cells or progenitor cells), 2) a complete search for all the groups of claims would be coextensive and would not be a serious search burden on the Office, 3) the requirement of choosing only one type of protein is improper as the proteins recited in the elected claims can be used as marker proteins (e.g. the elected fluorescent protein), 4) MPEP 806.04 states that if there is no serious search burden, the different inventions must be examined together. This is not found persuasive because of the following reasons.

Arguments directed to allegations of there being no serious search burden in examining the different groups together are off point in that the basis for restricting the different groups was a lack of unity under the rules of the PCT. Search burden is not relevant for determining restriction groupings for claims submitted in a 371 application, as is the instant application. In any case, assertions that the search would be coextensive and not a serious burden are not accurate as the search required for all groups would not be coextensive (e.g. transfection of nucleic acid/protein fusions versus just DNA or RNA). With regard to a contribution over the prior art, the examiner has demonstrated that methods were already known in the art for introducing substances comprising nucleic acids into mammalian neuronal stem or progenitor cells. Moreover, there is no evidence of record that the mechanisms for introduction of DNA,

RNA or nucleic acid/protein fusions into the recited neuronal progenitor cells are the same for each composition.

With regard to a requirement that applicant elect a single type of protein, the assertion that all of the claims are directed to nucleic acids encoding marker proteins is inaccurate. Claim 1, for example, has no limitation that the nucleic acid encodes a marker protein. Only a few of the elected claims are explicitly directed to the use of nucleic acids encoding marker proteins. For example, there is no support in the specification for the use a protein that activates proliferation, differentiation and/or lineage determination as a cell marker (e.g. claim 8). Such nucleic acids have the different property of allowing the amplification and/or differentiation of the desired progenitor cells as opposed to methods of selecting such cells. The examiner properly restricted nucleic acids encoding proteins of different functionality from one another as they have different uses (i.e. different special technical features). For these reasons, claim 8 is also withdrawn from consideration as being directed to nonelected inventions. There is support, however, for the concept of using a radioactively tagged nucleic acid as a marker. Therefore, since applicants elected a specific embodiment that is explicitly directed in the specification to identification of transfected neuronal stem or progenitor cells, and because radiolabeled nucleic acids are specifically contemplated by applicants for such methods, claim 13 has been rejoined with the elected invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-45 are pending in the instant application, with claims 5-6, 8, 15-22, 24-45 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a

nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7. **Claims 1-4, 7, 9-14 and 23 are under consideration to the extent they read on nucleic acids that can be used as markers for neuronal stem or progenitor cells (e.g. radiolabeled or encoding a marker protein such as B-galactosidase).**

Information Disclosure Statement

Receipt is acknowledged of information disclosure statements (IDS) filed on 1/3/2002 (Paper No. 5) and 7/13/2001 (Paper No. 1). The signed and initialed PTO Form 1449s corresponding to each IDS have been mailed along with this action.

Drawings

The drawings were received on 7/13/01. These drawings are accepted.

Claim Objections

Claims 1-4, and 7 are objected to because of the following informalities: each of the claims encompasses nonelected embodiments (i.e. nucleic acids that do not encode or are not themselves markers for selecting transfected neuronal stem or progenitor cells). Appropriate correction is required.

Claim 23 is objected to as being dependent upon a nonelected claim (i.e. claim 8).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7, 9-14 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are directed to methods of introducing a substance comprising a nucleic acid into mammalian neuronal stem or progenitor cells. Each of the claims comprises the limitation of "...wherein said nucleic acid **directly interacts** with the cell membrane of said cell or a component within said cell membrane *in vitro* whereby the substance comprising said nucleic acid is taken up by the cell via the **inherent transport mechanism** of the cell." (Examiner's emphasis added). The rejected claims encompass a neuronal stem or progenitor cell obtained from *any* mammalian source that must retain the functional capability of being transfected by a mechanism that involves the direct interaction of the nucleic acid with some component of the host cell.

The specification describes an experiment in the only working example where plasmid DNAs were transfected into rat progenitor cells isolated from the hippocampus (the sole working example described on pages 11-13). The specification merely demonstrates that the rat neuronal stem or progenitor cells are somehow competent for DNA transfection without the need for

treatments usually needed for transfection of mammalian cells (e.g. use of a protamine or viral carrier to allow receptor-mediated endocytosis). Kidney-derived Cos-7 cells did not exhibit such natural competency for the uptake of exogenous DNAs (e.g. page 12, lines 23-31). The concept of how a nucleic acid "directly interacts" with the cell membrane or component thereof is not clearly explained in the specification. The term "directly interacts" implies some sort of binding between the nucleic acid and some component within the cell membrane, but there is no explanation or evidence of any such binding anywhere in the instant specification. The question arises then, do the limitations of "directly interacting" and "inherent transport mechanism" specify a specific binding interaction by the DNA with a component of the cell membrane, or do they encompass any method whereby the progenitor cell is transfected with a nucleic acid so long as the DNA is take up by the targeted host cell? There is no actual evidence that the results observed for the cells used in the working example of the instant specification would satisfy the functional limitations of "direct interaction" in the recited methods of transformation. In any case, the specification does not provide a basis for one to envision the critical element of a specific component or components in the neuronal host cell membrane with which the nucleic acid "directly interacts" such that the nucleic acid is taken into the cell. As a result, there is no basis for one to extrapolate the findings described by the instant specification to mammalian neuronal stem or progenitor cells obtained from other sources than the rat.

The prior art appears to be silent with regard to the natural competency of neuronal stem or progenitor cells for taking up exogenously added nucleic acids. Therefore, the prior art does not offset the deficiencies of the instant specification with regard to describing even one specific

embodiment that satisfies the functional limitations of the nucleic acid "directly interacting" with a component of the cell membrane such that the DNA is taken up into the cell.

Given the lack of any evidence that the sole working example in the instant specification demonstrates an "direct interaction" between the nucleic acid and a component of the cell membrane (i.e. binding), and given the apparent lack of any description of such an inherent nucleic acid transport system in neuronal stem or progenitor cells in the prior art, the skilled artisan would not have been able to reliably envision a specific embodiment of this critical element of the claimed invention, much less enough specific embodiments to describe the broadly claimed genus of such mechanisms of DNA uptake in any neuronal stem or progenitor cells. Therefore, the skilled artisan would reasonably have concluded applicants were not in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7, 9-14 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of the phrase "...wherein said nucleic acid directly interacts with the cell membrane of said cell or a component within said cell membrane *in vitro* whereby the substance comprising said nucleic acid is taken up by the cell via the inherent transport mechanism of the cell..." are unclear. The concept of how a nucleic acid "directly interacts" with the cell membrane or component thereof is not clearly

explained in the specification. The term "directly interacts" implies some sort of binding between the nucleic acid and some component within the cell membrane, but there is no explanation or evidence of any such binding anywhere in the instant specification. The specification merely demonstrates that the rat neuronal stem or progenitor cells are somehow competent for DNA transfection without the need for treatments usually needed for transfection of mammalian cells (e.g. use of a protamine or viral carrier to allow receptor-mediated endocytosis), without any mechanistic explanation. The question then arises, does the cited phrase specify a specific binding interaction by the DNA with a component of the cell membrane, or does it encompass any method whereby the progenitor cell is transfected with a nucleic acid? It would be remedial to amend the claim language to explicitly indicate what kind of interaction with the host cell membrane is required in order to satisfy the functional limitations of the claim (e.g. actual binding of the nucleic acid to some component of the cell membrane or some sort of passive transfer of the nucleic acid across the membrane that does not require actual binding of the DNA to a component of the cell membrane).

Claim 2 is vague and indefinite in that it is unclear the nature and number of steps required in order to generate a "derivative" of an adult cell in the context of the claimed invention. The term implies an indirect approach to obtaining the desired host cell that may result in undefined changes in the structural/functional nature of the obtained cell. It would be remedial to amend the claim language to "obtained from", which implies a much more direct method of providing the recited host cell.

Claim 3 is vague and indefinite in that the metes and bounds of the term "humid atmosphere" are unclear. How humid does the atmosphere have to be in order to qualify as

"humid"? The rejected claim and specification do not spell out the exact level of humidity required in order to satisfy the cited claim limitation.

Claim 7 is vague and indefinite in that the metes and bounds of the words "specific cDNA" are unclear. In what sense is the recited cDNA "specific"? It would be remedial to amend the claim language to explicitly recite in what way the cDNA is "specific".

Claims 9-11 recite the phrase "gives rise to", which is inherently vague and indefinite in that it merely recites a desired outcome without any correlation to structure or function (e.g. encoding a detectable signal). It would be remedial to amend the claim language to more clearly indicate the structural/functional relationship with the recited composition that "gives rise to" a particular outcome (e.g. where a composition "comprises" or "encodes" a detectable signal).

Claim 13, dependent upon claim 11, recites that the detectable signal is due to a radioactively tagged nucleic acid. Claim 11, however, recites that the peptide or protein encoded by the transfected nucleic acid gives rise to a detectable signal. It is unclear how the detectable signal can be due both to the radioactively tagged nucleic acid and to a marker protein or peptide (e.g. a fluorescent protein). Thus, it is unclear whether claim 13 is meant to specify that there are two detectable signals (i.e. radioactive and a protein signal), or if claim 13 is directed to a different cell labeling technique wherein the label is a radioactive one incorporated directly into the transfected nucleic acid. It would be remedial to amend claim 13 to clearly indicate which of the possibilities for labeling is intended (i.e. labeling with both nucleic acid and protein, or just with a nucleic acid).

Claim 23 recites the limitation that the detectable signal allows for testing or an expressed protein or signal comprised within or encoded by the transfected nucleic acid. It is unclear what

is intended by the terms "testing" and "screening". Do the terms refer to the ability to use the protein or signal in a methodology to determine, for example, if certain compounds affect the cell fate (i.e. determination) of transfected cells, or do the terms simply mean that one can test or screen for the presence of cells comprising the protein or label? If the latter is the case, then it is unclear how the cited terms further limit a claim reciting the limitation that the transfected cells comprise a detectable signal.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejected claims are directed to methods of introducing a substance comprising a nucleic acid into mammalian neuronal stem or progenitor cells. Each of the claims comprises the limitation of "...wherein said nucleic acid **directly interacts** with the cell membrane of said cell or a component within said cell membrane *in vitro* whereby the substance comprising said nucleic acid is taken up by the cell via the **inherent transport mechanism** of the cell." (Examiner's emphasis added). As indicated above, the concept of how a nucleic acid "directly interacts" with the cell membrane or a component thereof is not clearly explained in the specification and, thus, it is unclear whether the transfected DNA must necessarily bind a component of the target host cell's membrane in order to be transferred to the interior of the host

cell (e.g. see the 112 2nd rejection of claim 1 above). Therefore, a reasonable interpretation of the claim language of the rejected claims is that there is no limitation that the transfected DNA actually binds to a component of the cell membrane such that it is transferred into the cell interior (e.g. receptor-mediated endocytosis). The following rejection is directed to such embodiments.

Claims 1, 7, 9-11, 14 and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al (U.S. Patent No. 6,001,654 A; see the entire patent).

The '654 patent teaches methods for producing a population of mammalian neurons and/or smooth muscle cells comprising contacting at least one mammalian neural stem cell with a culture medium containing one or more growth factors from the TFG-B superfamily (e.g. Abstract; column 3, lines 25-35). The specification teaches that various methods for transforming mammalian cells are known in the art (e.g. DEAE-mediated transfer, calcium phosphate-mediated transfer, viral vectors, etc.; column 7, lines 13-27; column 19, lines 28-column 20, line 32). For example, the patent teaches that neuronal crest stem cells can be transfected via the calcium-phosphate-mediated precipitation/transfection protocol with DNAs encoding an immortalization gene or genes (e.g. v-myc, T antigen, etc.) and/or a cell marker (B-galactosidase) (e.g. column 19, lines 28-column 20, line 32).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
GERRY LEFFERS
PRIMARY EXAMINER
Examiner
Art Unit 1636